REMARKS

Status of the claims

Claims 37-41 are pending and under consideration in this application. All the claims under consideration stand rejected. Claims 37, 38, and 40 are cancelled herein without prejudice to their being pursued in a separate application. Claims 44 and 45, which are supported by the specification (e.g., at page 9, line7, to page 13, line 4, and Examples 7 and 9), have been added. After entry of the amendments made herein, claims 39, 41, 44, and 45 will be pending and under consideration in this application. None of the amendments made herein add new matter.

35 U.S.C. § 112. second paragraph, rejections

Claims 37-41 stand rejected as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter that the Applicants regard as the invention.

Applicants respectfully submit that the rejection is moot with respect to claims 37, 38, and 40, because these claims have been cancelled.

From the comments on page 3, lines 8-13, of the Office Action, Applicants understand the Examiner's position to be that claim 39 is vague and indefinite because it fails to indicate how a normal concentration of albumin is correlated with an increased level of L-PGDS. Applicants disagree with this position but, in the interest of expediting prosecution of the present application, have amended the claim both in form and substance to further clarify it.

As pointed out in the specification, the method of the invention is a new and more sensitive way of testing for relatively early renal disease (e.g., see page 9, line 7, to page 13, line 4 and Examples 4, 5, 7, and 9). Hence, subjects having early renal disease and testing negative by other criteria (e.g., urinary albumin and urinary type IV collagen levels), show elevated levels L-PGDS. Thus, while in claim 39 the order in which the testing is done is not necessarily in the order stated, in the interest of clarity, the claim has been amended to recite the testing for albumin before the recitation of the testing for L-PGDS. Moreover, a clause has been added indicating that the determination of a normal urinary albumin level in the subject fails to detect renal disease in the subject. The subject is also tested for the level of L-PGDS in its urine. An

elevated level of L-PGDS in the subject indicates that the subject does in fact have early renal disease.

Applicants believe that the above amendments to claim 39 provides it with greater clarity and therefore respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

35 U.S.C. § 103 (a) rejection

Claims 37-41 stand rejected as allegedly being unpatentable over Hoffman et al. in view of Katzberg et al.

Applicants respectfully submit that the rejection is moot with respect to claims 37, 38, and 40, because these claims have been cancelled.

From the comments on page 5, line 5, to page 7, line 2, of the Office Action, Applicants understand the Examiner's position to be that it would have been obvious in view of Hoffman et al. and the knowledge of those skilled in the art to have tested subjects for levels of L-PGDS, even in patients having normal urine albumin levels. Applicants disagree with this position.

Hoffman et al. is silent as to testing for L-PGDS in the urine of patients with any renal disease, let alone early renal disease. Even the statement in Hoffman et al. referred to in the Office Action (page 5, lines 17-18) as indicating that serum levels of L-PGDS may be useful in early diagnosis of renal disease is at best luke-warm in regard to this possibility. The relevant text from Hoffman et al. states "We suppose that especially in early diagnosis of renal diseases . . . it may become a much more reliable and sensitive parameter" (page 505, column 1, paragraph 2; underlining added). Thus, Hoffman et al. indicates that at some unknown time in the future it is possible that early diagnosis of renal disease may be done by measuring serum L-PGDS levels. Applicants respectfully submit that this statement, contrary to the assertion on page 5, lines 18-20, of the Office Action, constitutes merely an invitation to try diagnosing early renal disease by measuring serum L-PGDS levels without the least assurance of success.

However, even if Hoffman et al. was to teach diagnosing early renal disease by measuring serum L-PGDS, nowhere does it disclose or even suggest doing so with urine. As

stated in the Office Action (page 6, lines 2-3), "Hoffman et al. specifically teaches that in renal diseases that the elimination of proteins through the kidney is disturbed resulting in elevated concentrations of proteins." As these elevated levels of proteins were in blood and ultrafiltrate (Hoffman et al., e.g., Abstract), the disturbance in elimination of the proteins through the kidney resulting in increased serum and ultrafiltrate levels of L-PGDS could well have been accompanied by no increase, or even a decrease, in the level of L-PGDS in urine. Thus, even if there were any suggestion in Hoffman et al. to test for early renal disease by measuring urinary L-PGDS levels (which, as pointed out above, there is not), such a suggestion would have been without any assurance of success.

Moreover, assuming again for the sake of argument that Hoffman et al. taught testing for early renal disease by measuring urine L-PGDS levels (which as pointed out above there is not), it contains no disclosure or suggestion of doing it as well as testing for levels of albumin or type IV collagen. Katzberg et al. provides no remedy for this defect because, while it does point out that "[e]ven moderate degrees of renal insufficiency can be masked by a serum creatinine concentration falling within the normal range" (column 1, lines 24-26), this statement is made in connection with creatinine (the subject of cancelled claims 37 and 40) and the reference makes no such statements regarding albumin (the subject of claims 39 and 41) or type IV collagen (the subject of new claims 44 and 45).

In addition, while it is possible that "it is known in the art that albumin and proteinuria are associated with kidney disease" (Office Action, page 7, lines 1-2), there is no evidence that one ordinarily skilled in the art would have combined any hypothetical suggestion by Hoffman et al. of testing for early-stage renal disease by measuring urine L-PGDS levels with measuring urine albumin and/or type IV collagen levels. Indeed, increased urinary albumin and collagen IV levels were previously considered to be markers of early renal disease. Thus, for example, Massary et al. (Massary & and Glassock's Textbook of Nephropathy, 4th ed. Lippincot Williams and Wilkins, Philadelphia (2001), pages 1785-1786; copy enclosed as Exhibit A) states that "[t]he specific detection of small quantities of albumin (microalbuminuria) may be useful in the evaluation of early stages of diabetic nephropathy." (page 1786, left column, from 11th to 13th

line from the bottom). Moreover, Seldin et al. (The Kidney: Physiology and Pathophysiology, 3rd ed., Lippincot Williams and Wilkins, Philadelphia (2000), page 2279; copy enclosed as Exhibit B) states "[t]his study suggests that microalbuminuria is not simply a predictor of diabetic nephropathy but rather is a marker of early nephropathy." (page 2279, left column, 18th to 20th line from the bottom. In addition, with respect to type IV collagen, Hayashi et al. (Diabetic Medicine 9:366-370 (1992); copy enclosed as Exhibit C) states that "[u]rinary concentrations of type IV collagen may have a role as an indicator or early diabetic nephropathy." (Abstract, lines 9-11). Thus, prior to the teaching of the present application, one skilled in the art would not have been motivated to test for urine levels of albumin (or type IV collagen) as well as L-PGDS, even if Hoffman et al. had taught testing for urine levels of L-PGDS (which as argued above it did not). In light of the teaching at the time, it is likely that such an artisan would have used conventional tests (e.g., for urine albumin and/or type IV-collagen levels), would likely have considered a normal level of urinary albumin (or type IV collagen) as determinative of the absence of early renal disease, and would have been unlikely to seek further confirmation of such absence. For the reasons given above, it is extremely unlikely that he or she would have been persuaded by the disclosure of Hoffman et al. to test the urine of relevant subjects for their levels of L-PGDS.

It was the instant application that taught doing so for the first time. Thus, the instant specification states that "it has become evident that L-PGDS can be an indicator of renal diseases which is comparable to serum creatinine, urinary albumin and urinary type-IV collagen used so far." (page 18, lines 24-27). More importantly, the specification states: "This indicates that extremely early-stage diabetic nephropathy which is undetectable by determining urinary albumin or urinary type-IV collagen can be detected by determining urinary L-PGDS" (page 27, lines 5-9) and "These results indicate that extremely early-stage diabetic nephropathy which is undetectable by determining urinary albumin or urinary type-IV collagen can be detected by determining urinary L-PGDS." (page 28, lines 22-26).

For all the reasons given above, Applicants submit that one of ordinary skill in the art would not have been motivated by combining the teachings of the cited art and his or her general knowledge to perform the methods of the instant claims.

Moreover, Applicants submit that the findings of the instant application showing an increased urinary L-PGDS level to be a marker of early renal disease, especially in combination with the observation of a normal urinary albumin or type IV collagen level, constitute surprising and unexpected results and, as such, provide additional indicia of non-obviousness of the instant claims.

In light of the above considerations, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In summary, for the reasons set forth above, Applicants maintain that the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action, and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a request for an automatic extension of time and a check in payment of the extension in time. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 11283-009001.

Respectfully submitted,

Date: 2/7/06

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